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Risk factors for medullary thyroid carcinoma: a pooled analysis

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Abstract

Objective: To investigate risk factors for medullary thyroid cancer (MTC).
Methods: We conducted a pooled analysis of 14 case–control studies from Europe, North America, and Asia, including 67 medullary cancers (43 women and 24 men) diagnosed in ten studies. Of the original 4776, we selected five controls per case matched on study, gender, and age. The pooled odds ratios (OR) were estimated using conditional logistic regression.
Results: Education, weight, and body mass were not associated with MTC, but a significant positive relationship was seen with height (OR = 2.6 for highest *vs* lowest tertile). Significant excess risks were associated with a history of thyroid nodules (OR = 12), hypertension (OR = 2.3), gallbladder disease (OR = 4.3), and allergies (OR = 2.2). Among current smokers, a decreased risk of MTC was observed with increasing number of cigarettes. The risk was significantly elevated among women having a first birth after age 25 years, but no clear pattern emerged for other reproductive factors.
Conclusions: Although the number of MTC was small, we detected several significant associations, including prior thyroid and other diseases.

Introduction

Medullary thyroid carcinoma (MTC) is a rare disease, accounting for less than 10% of all thyroid cancers [1]. Although the majority of thyroid cancers originate from follicular epithelial cells, MTC arises from parafollicular calcitonin-secreting cells (C-cells) of the thyroid gland. Because of its rarity, epidemiologic data on MTC are scarce.

Approximately 80% of patients develop a sporadic form of MTC, while the remaining cases are inherited as an autosomal dominant trait with age-related penetrance and variable expression [2, 3]. Sporadic MTC tends to be unifocal, whereas hereditary MTC is generally multifocal. Three hereditary forms of MTC have been described. In multiple endocrine neoplasia type 2A (MEN 2A), MTC is associated with pheochromocytoma and parathyroid hyperplasia or adenoma. In multiple endocrine neoplasia type 2B (MEN 2B), MTC is associated with pheochromocytoma, multiple

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mucosal neuromas, and developmental abnormalities including marfanoid habitus [4]. Familial medullary thyroid carcinoma (FMTC) may also occur as the sole manifestation without other endocrine anomalies [5]. All syndromes involving MTC result from germline mutations of the *ret* proto-oncogene located on chromosome 10 [4, 6–8]. Although nearly all cases of FMTC and MEN 2A are associated with familial occurrence, a high proportion of MEN 2B cases are sporadic and result from *de-novo* germline mutations [9].

The female-to-male ratio in different series of MTC ranges from 1 to 1.5 as compared to a 3-fold female excess for papillary or follicular thyroid carcinomas [10]. The tumors may arise at any age, but although the onset of inherited cases is often below age 30 years, the mean age at diagnosis is in the fifth decade [10]. The international variation of MTC is limited, with the highest incidence (>2 per million per year) reported in Western countries, probably from diagnostic and reporting practices [11]. In an effort to identify the risk factors for MTC, we conducted an international pooled analysis using the original data sets from all known case–control studies of thyroid cancer.

Table 1. Distribution of medullary thyroid cancers and controls by study center, gender and age

Variable	Cases (%) (n = 67)	Controls (%) (n = 335)
Study center [ID]		
Los Angeles [LA]	5 (7)	25 (7)
Hawaii [HA]	2 (3)	10 (3)
Connecticut [CT]	9 (13)	45 (13)
Hiroshima and Nagasaki, Japan [JP]	2 (3)	10 (3)
Shanghai, China [SH]	4 (6)	20 (6)
Southeastern Sweden [SS]	3 (4)	15 (4)
Northern Sweden [NS]	7 (10)	35 (10)
Northern Italy [IT]	18 (27)	90 (27)
Vaud, Switzerland [SW]	7 (10)	35 (10)
Athens, Greece [GR]	10 (15)	50 (15)
Gender		
Men	24 (36)	120 (36)
Women	43 (64)	215 (64)
Age (years)		
<30	17 (25)	78 (23)
30–39	6 (9)	39 (12)
40–49	18 (27)	88 (26)
50–59	13 (19)	67 (20)
≥60	13 (19)	63 (19)

Materials and methods

We obtained the original data from 14 case–control studies of thyroid cancer that were conducted between 1974 and 1992, and were identified through MEDLINE searches or personal knowledge. The study methods are described in detail by Negri *et al.* [12]. Of the 2725 thyroid cancer cases in the pooled data set (2247 women, 478 men), 67 cases (2%) had medullary thyroid carcinoma (43 women, 24 men). The cases came from ten of the 14 study centers participating in the pooled analysis (Table 1). Three of the 14 studies excluded medullary cancers, while one study classified tumors only as papillary or non-papillary.

We selected five matched controls per case from the original 4776 controls. Controls were matched by gender, age, and study center. For the Hawaii study subjects we also matched on ethnic group. If the study was individually matched, we first selected the matched control(s) and then controls of the same sex, with preference given to those closest in age to the case, until five controls were identified. If there were more than five potential controls, we randomly selected five.

Since some study centers did not collect information on all epidemiologic variables, certain analyses were based on less than the total number of cases and controls, as shown in Tables 2–4. For height and weight we computed tertiles based on the distribution of controls separately for men and women. Because mean height and weight varied across study centers [13], we also analyzed the anthropometric data using study-specific tertiles based on the distribution of all controls in the original studies. In addition, we standardized the anthropometric variables using study- and sex-specific means and standard deviations. The three approaches yielded very similar results, and we present only the first one.

Conditional logistic regression models were used to obtain estimates of the pooled odds ratios (ORs) and 95% confidence intervals (CIs) [14]. A linear term for age was included in the models. When possible, we evaluated variables using both categorical and continuous terms in separate models. For ordered categories a test for linear trend in risk was performed. The interaction of trends and continuous terms with sex and age was evaluated by means of the −2 log-likelihood chi-square test [14]. In supplemental analyses, ORs were estimated separately for men and women, and for subjects below and above 45 years of age.

Since not all studies collected information on all variables, including all significant factors in the same model would result in a small number of cases with non-missing values. To investigate mutual confounding, we included in turn two of the significant factors in a model. The ORs estimated in these models were similar to those presented.

Table 2. Distribution[a] of medullary thyroid cancer cases and controls and odds ratios for education, anthropometric variables, and smoking

Variable (cases:controls)[b]	No. of cases	No. of controls	OR[c]	95% CI[d]
Education (55:274)				
Low	13	72	1[e]	
Intermediate	22	105	1.17	0.52–2.66
High	20	97	1.15	0.46–2.88
			$\chi^2_{trend} = 0.07$, $p = 0.79$	
Height (67:335)				
Low	14	104	1[e]	
Intermediate	21	124	1.31	0.62–2.78
High	32	107	2.55	1.21–5.38
			$\chi^2_{trend} = 6.64$, $p = 0.01$	
Per 5 cm increase			1.33	1.08–1.63
Weight (67:335)				
Low	25	117	1[e]	
Intermediate	19	115	0.77	0.39–1.50
High	23	103	1.07	0.55–2.06
			$\chi^2_{trend} = 0.04$, $p = 0.84$	
Per 5 kg increase			0.97	0.86–1.10
Body mass index (67:335)				
Low	28	110	1[e]	
Intermediate	20	115	0.65	0.33–1.29
High	19	110	0.65	0.33–1.28
			$\chi^2_{trend} = 1.46$, $p = 0.23$	
Per 5 kg/m^2 increase			0.73	0.50–1.05
Smoking status (67:335)				
Never smoked	35	158	1[e]	
Current smoker	21	128	0.73	0.39–1.37
Former smoker	11	49	0.97	0.44–2.14
Duration of smoking[f]				
<25 years	11	51	1.26	0.50–3.17
≥25 years	9	69	0.40	0.15–1.02
			$\chi^2_{trend} = 2.57$, $p = 0.11$	
Per 10 years increase[g]			0.56	0.12–2.61
No. of cigarettes/day[f]				
<15	12	40	1.31	0.61–2.79
≥15	8	84	0.30	0.12–0.76
			$\chi^2_{trend} = 4.63$, $p = 0.03$	
Per 10 cigarettes increase[g]			0.76	0.41–1.39

[a] Information was missing in three studies (JP, SS, NS) for education.
[b] Number of cases and controls with non-missing values.
[c] Odds ratios (OR) estimated from conditional regression models, including a linear term for age.
[d] 95% confidence interval.
[e] Reference category.
[f] Former smokers excluded; reference: never smokers.
[g] Only current smokers.

Results

Table 1 shows the distribution of cases and controls by study center, gender, and age. Since cases and controls were matched on study, sex, and age, the distribution of cases and controls was very similar. Sixteen cases (24%) came from studies conducted in the United States (LA, HA, CT), 6 (9%) from Asia (JP, SH), 10 (15%) from Sweden (SS, NS) and 35 (52%) from southern Europe (IT, SW, GR). The mean age of the MTC cases was 44.4 years. Forty-three (64%) of the cases were women, and 23 (34%) were below age 40.

The distribution of cases and controls and the ORs for education, anthropometric factors, and smoking are presented in Table 2. Education, weight, and body mass were not associated with MTC, but a significant trend

Table 3. Distribution[a] of medullary thyroid cancer cases and controls and odds ratios for selected medical history variables

Variable (cases:controls)[b]	No. of cases	No. of controls	OR[c]	95% CI[d]
Goitre (57:285)				
No	53	278	1[e]	
Yes	4	7	3.07	0.85–11.1
Thyroid nodules and adenomas (47:235)				
No	42	232	1[e]	
Yes	5	3	12.1	2.26–64.7
Hyperthyroidism (67:335)				
No	65	329	1[e]	
Yes	2	6	1.66	0.31–8.81
Hypothyroidism (54:270)				
No	53	262	1[e]	
Yes	1	8	0.60	0.07–5.12
Cancer (55:275)				
No	52	263	1[e]	
Yes	3	12	1.47	0.36–5.91
Allergies (48:240)				
No	34	198	1[e]	
Yes	14	42	2.19	1.01–4.74
Diabetes (59:295)				
No	58	289	1[e]	
Yes	1	6	0.84	0.10–6.97
Hypertension (51:255)				
No	40	227	1[e]	
Yes	11	28	2.33	1.03–5.27
Gallbladder disease (45:225)				
No	38	214	1[e]	
Yes	7	11	4.28	1.39–13.2
Radiotherapy (63:314)				
No	59	297	1[e]	
Yes	4	17	1.21	0.39–3.80
Family history of benign thyroid conditions (43:219)				
No	38	200	1[e]	
Yes	5	19	2.05	0.52–8.12

[a] Information was missing in one study (GR) for goiter, in three (SS, NS, GR) for thyroid nodules and adenomas, in two (SS, GR) for hypothyroidism, in two (JP, GR) for cancer, in three (LA, SH, GR) for allergies, in three (HA, JP, SH) for diabetes; in five (LA, HA, JP, SH, SS) for hypertension, in five (LA, HA, CT, JP, SH) for gallbladder disease, and in one (SH) for radiotherapy.

[b] Number of cases and controls with non-missing values.

[c] Odds ratios (OR) estimated from conditional regression models, including a linear term for age.

[d] 95% confidence interval.

[e] Reference category.

was found between height and MTC risk. Compared with the lowest tertile for height, the ORs were 1.3 (95% CI: 0.62–2.8) and 2.6 (95% CI: 1.2–5.4) in the second and third tertile. The corresponding ORs were 1.2 (95% CI: 0.51–2.9) and 1.8 (95% CI: 0.73–4.6) for women, and 1.5 (95% CI: 0.35–6.3) and 4.7 (95% CI: 1.2–18) for men. Risk increased 33% for each 5 cm increment in height, and the slope was similar in the two sexes (39% in men and 29% in women). Compared with non-smokers there was a reduced risk for current smokers (OR = 0.73, 95% CI: 0.39–1.4) but not former smokers (OR = 0.97, 95% CI: 0.44–2.1). The inverse relation to smoking was most prominent in long-term (OR = 0.40, 95% CI: 0.15–1.02) and heavy smokers (OR = 0.30, 95% CI: 0.12–0.76), in the absence, however, of a monotone dose–risk relation.

In Table 3 the ORs for self-reported medical history variables are presented. The OR for thyroid nodules or

Table 4. Distribution[a] of female medullary thyroid cancer cases and controls and odds ratios for selected menstrual and reproductive variables

Variable (cases:controls)[b]	No. of cases	No. of controls	OR[c]	95% CI[d]
Age at menarche (41:215)				
<13	10	70	1[e]	
13–14	21	98	1.50	0.65–3.42
≥15	10	47	1.54	0.55–4.31
			$\chi^2_{trend} = 0.78$, $p = 0.38$	
Menopausal status (35:180)				
Pre/peri	19	108	1[e]	
Post	16	72	2.24	0.54–9.25
Parity (36:180)				
Parae	25	129	1[e]	
Nulliparae	11	51	1.32	0.46–3.76
Number of births (36:180)				
Nulliparae	11	51	1[e]	
1–2	17	73	0.89	0.30–2.60
≥3	8	56	0.57	0.17–1.91
			$\chi^2_{trend} = 1.03$, $p = 0.31$	
Per birth			0.85	0.65–1.12
Number of miscarriages (36:180)				
0	27	139	1[e]	
1	3	22	0.70	0.19–2.57
≥2	6	19	1.57	0.55–4.49
			$\chi^2_{trend} = 0.40$, $p = 0.53$	
Per miscarriage			1.14	0.82–1.58
Number of induced abortions (36:180)				
0	32	156	1[e]	
1	2	16	0.62	0.13–2.92
≥2	2	8	1.26	0.20–7.97
			$\chi^2_{trend} = 0.02$, $p = 0.89$	
Per induced abortion			0.89	0.42–1.88
Age at first birth (34:176)				
<25	9	81	1[e]	
25–29	7	30	2.17	0.74–6.39
≥30	7	14	5.64	1.74–18.3
Nulliparae	11	51	2.42	0.73–8.09
			$\chi^2_{trend} = 8.57$[f], $p = 0.003$	
Per 5 years increase[e]			2.02	1.28–3.17

[a] Information was missing in two studies (SS, NS) for menopausal status, parity, number of miscarriages and induced abortions, and age at first birth.
[b] Number of cases and controls with non-missing values.
[c] Odds ratios (OR) estimated from conditional regression models, including a linear term for age.
[d] 95% confidence interval.
[e] Reference category.
[f] Nulliparae excluded.

adenomas was 12.1 (95% CI: 2.3–65), while the ORs for goiter and hyperthyroidism were 3.1 (95% CI: 0.85–11) and 1.7 (95% CI: 0.31–8.8), respectively. Significantly elevated risks were also associated with hypertension (OR = 2.3; 95% CI: 1.03–5.3), gallbladder disease (OR = 4.3; 95% CI: 1.4–13), and allergies (OR = 2.2; 95% CI: 1.01–4.7). We also examined the risk associated with a self-reported history of radiotherapy (OR = 1.2; 95% CI: 0.39–3.8), but this variable was not well defined in some studies, and the reason for treatment was not always provided. A family history of benign thyroid disease was reported more often by cases than controls (OR = 2.1; 95% CI: 0.52–8.1), especially among cases less than 45 years of age at diagnosis (OR = 2.9; 95% CI: 0.43–17) compared with older cases (OR = 1.3; 95% CI: 0.14–12) (data not shown).

Table 4 shows the ORs for menstrual and reproductive variables. No clear pattern of risk emerged for age

at menarche, menopausal status, number of miscarriages, or induced abortions. A non-significant increase in risk was seen for nulliparous compared with parous women (OR = 1.3; 95% CI: 0.46–3.8), while the risk decreased with increasing number of births (OR per additional birth, 0.85; 95% CI: 0.65–1.1). More pronounced was the effect of age at first birth. Compared with women whose first birth occurred before age 25, the ORs for women having a first birth between 25 and 29 years and 30+ years were 2.2 (95% CI: 0.74–6.4) and 5.6 (95% CI: 1.7–18), respectively. The OR for a 5-year increase in age at first birth was 2.0 (95% CI: 1.3–3.2). The risk for nulliparous women was 2.4 (95% CI: 0.73–8.1) relative to women who delivered before age 25.

The analyses described above were carried out separately for two age groups (above and below 45 years), and for men and women when appropriate. Due to small numbers, heterogeneity between subgroups is difficult to detect. However, the findings appeared consistent among subgroups.

Discussion

Although this international pooled analysis of MTC cases from ten case–control studies yielded only 67 cases, some significant associations were found. There was an increased risk with increasing height, and significant positive associations with a history of benign thyroid diseases, hypertension, allergies, and gallbladder disease. In addition, there were suggestive reductions in risk associated with current smoking and, among women, with having a live birth before age 25 years. In reporting these results, however, several limitations of our study should be considered. In addition to the small number of total cases, our pooled analysis was based on original data that varied in detail by study center, so that even smaller numbers were used to evaluate some variables. Furthermore, since we investigated a large number of potential risk factors, some associations may represent chance findings due to the multiple comparisons that were made in our analyses.

A complete pathology review, for all thyroid cancer histologies, was conducted in the study subjects from Hawaii, Connecticut, Shanghai, Northern Sweden, and Vaud. In an attempt to determine the adequacy of the medullary cancer diagnoses at the other study centers we compared the percentage distribution of thyroid cancer cases by histologic type in the pooled analysis with that provided in *Cancer Incidence in Five Continents* [11] for the study areas (except in Sweden and Greece where no histologic breakdown was available). Although the distributions were consistent, the percent of MTC in the pooled analysis tended to be somewhat lower than the reported incidence ratios, suggesting an underascertainment of MTC cases in the pooled analysis of all thyroid cancers. If indeed underascertainment of MTC cases has occurred, we were not able to establish if it was due to tumors being misclassified as to the type or missed altogether.

If we exclude the nine female cases from the two studies that collected data only on women (LA and SH), the female:male ratio is 1.4, compatible with that observed in case series [10].

We did not have clinical or genetic data to clearly distinguish sporadic from familial cases of MTC. Information on family history was available for 30 MTC cases and 150 controls from six of the 10 study centers. Only one case and no controls reported a history of thyroid cancer in first-degree relatives. Since MTC is familial in about 20% of cases, we would have expected approximately six familial cases. The deficit in our study may be due to restriction of family data to first-degree relatives, incomplete penetrance of the genes, or lack of awareness of cancer occurrence in relatives. A weak positive association was noted, however, for a family history of benign thyroid disease. Since hereditary cases usually have an early age at onset, we replicated our analyses for cases diagnosed below and above age 45, but results were similar in the two age groups. Also, for the 17 cases diagnosed before age 30, there were no exceptional features in terms of height or medical conditions. Overall, the mean age in our study was 44 years, which is similar to previous clinical surveys [15, 16].

Most notable in our study was the 12-fold risk of MTC associated with a history of thyroid nodules or adenomas. In addition, non-significantly increased risks were associated with a reported history of goiter or hyperthyroidism, but not hypothyroidism. In our full pooled analysis of thyroid cancer [17], elevated risks of papillary and follicular cell types were associated with a history of benign thyroid nodules (OR over 20) and goiter (OR about 6). It is possible that cases tended to recall prior diseases, particularly of the thyroid, more often than controls. However, we observed no association with hypothyroidism, and there is no obvious reason to suggest differential recall bias for the self-reporting of various thyroid diseases. Close medical surveillance in people with benign thyroid disease might explain part of the excess, but the long period between the diagnosis of benign thyroid disease and MTC found for many cases ($\geq$5 years for most cases) suggests that surveillance is less likely an explanation than pre-existing hyperplasia of C-cells that is characteristic of the natural history of MTC.

An increased risk of about four-fold was associated with gallbladder disease in both sexes. The mechanism is unclear but may be a consequence of diagnostic work-ups for gastrointestinal symptoms resulting from high levels of calcitonin released by MTC, or possibly from multiple mucosal neuromas of the digestive tract in MEN 2B [3]. These neuromas may occasionally obstruct the biliary passages [18]. In addition, cholelithiasis has been reported in about 15–20% of pheochromocytoma patients [19], perhaps related in part to detection of incidental disease by abdominal imaging for adrenal tumors.

The excess risk of MTC associated with hypertension is intriguing in view of the occurrence in MEN 2A and 2B of pheochromocytomas, which induce hypertension by release of catecholamines [19]. In addition, the secretion of calcitonin and other vasoactive compounds (e.g. serotonin and prostaglandins) by MTC may be involved to some extent in blood pressure fluctuations. More difficult to interpret is the relation we found between allergy and MTC, since in most studies specific allergic conditions were recorded. Although recall bias may be involved, it is possible that some vasoactive compounds released by MTC contribute to cutaneous or respiratory symptoms resembling allergic states.

A positive association between height and MTC risk was seen in both sexes and across all study centers. While the precise reason is unclear, it is noteworthy that patients with MEN 2B often have skeletal abnormalities including a marfanoid body shape (tall and slender with long extremities). However, height was directly related to all thyroid cancers in our pooled analysis [13], although the association was weaker than in the present article.

Our pooled analysis also suggested a reduced risk of MTC among current smokers, and particularly long-term and heavy smokers. Similar results have been reported for all thyroid cancers in our pooled analysis, and in a recent study of papillary thyroid carcinoma among US women [20] and in a study from eight Canadian provinces, including a total of 1224 thyroid cancer cases, 45 of which were medullary [21]. Smoking may exert a protective effect on thyroid neoplasia through a hormonal mechanism, such as a decrease in TSH secretion or an anti-estrogenic effect [22–24]. However, the excess of medical conditions associated with MTC might also result in avoidance or cessation of smoking. Another protective factor suggested by our study was parity, particularly first birth at an early age. This effect was present but less pronounced in our pooled analysis of all thyroid cancers combined [25].

In summary, this epidemiologic study of MTC pointed to several risk factors, including pre-existing thyroid disease, height, hypertension, gallbladder disease, and allergies, as well as possible protective factors including smoking, parity, and early age at first birth. Although there was little evidence for familial occurrences in our study, it is known that a significant proportion of apparent sporadic cases has MEN type 2 syndrome either inherited, or have *de-novo* germline mutations of the RET proto-oncogene [26–29]. Thus, while some of the factors associated with MTC risk appear to be early manifestations of disease (*e.g.* pre-existing thyroid disease due to C-cell hyperplasia), other factors such as hypertension and height may be indicators of an underlying MEN type 2 syndrome.

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